oligonucleotides according to claim1. Claims 2-7, 21-35, 37-39 and 51-206 have been cancelled without prejudice to their prosecution in a continuation application.

Applicants wish to thank Examiner Weiss for the telephonic interview granted to Applicants' undersigned representative on 16 December 1996. During the interview it was agreed that Applicants would limit the claims to oligonucleotides that bind to a region of secondary structure in the epsilon region of the HBV genome. Based upon the unpredictability of the ability of oligonucleotides to inhibit gene expression when secondary structure is present in the target region, Applicants' representative was informed that such an amendment would receive favorable consideration and that the most pertinent art rejections, based on Offensberger *et al.*, would be withdrawn. In addition, Applicants' representative was informed that the rejections based upon probe art (Bresser *et al.*) would also be withdrawn as a result of such amendment, because it would not be obvious to target a region containing secondary structure as a site for binding a probe.

Applicants have amended claim 1 to specify only those oligonucleotides that bind to a region of secondary structure in the epsilon region of the HBV genome and inhibit HBV replication. Support for this amendment is found in the specification at page 15, line 30, page 29, lines 1-3 and in Figures 1, 3 and 11. Applicants have also added claim 225 to claim the 14 specific examples of such oligonucleotides which are specifically disclosed in the specification and which collectively span the entire epsilon secondary structure region. Support for this amendment is found in the specification in Figure 3, in which the claimed oligonucleotides are shown as HBV43, HBV88, HBV46, HBV1, HBV2, HBV5, HBV3, HBV4, HBV92, HBV101, HBV94, HBV71, HBV93 and HBV6. Please see also Table 1 on page 16, which correlates these oligonucleotide designations to the SEQ ID NOS recited in new claim 225. All claims to oligonucleotides complementary to targets outside the epsilon region have been cancelled. Applicants respectfully submit that these amendments overcome the prior art rejections of sections 5 and 7 of the Office Action mailed 29 November 1996.

For the sake of completeness of this response, Applicants further present the following brief explanation of why these amendments further obviate the less pertinent rejections of sections 1-4 and 6 of the Office Action. First, the rejection over the Wu *et al.* references (section 1 of Office Action) has been overcome by the removal of the target region taught by Wu *et al.* from claim 1 and the cancellation of any dependent claim specifying oligonucleotides complementary to such target region. Second, the rejection over Wu *et al.* in view of Ono *et al.* (section 2 of Office Action) has been overcome by limiting the claims to the target region having secondary structure which renders the results of the instant application unexpected (see last paragraph of section 2 of Office Action). The rejection over Wu *et al.* in view of Uhlmann *et al.* (section 3 of Office Action) is similarly overcome, since the addition of the Uhlmann *et al.* reference adds nothing which suggests the claimed target region. The rejection over Oh *et al.* in view of Ono *et al.* (section 4 of Office Action)

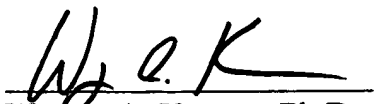
has been overcome by removal of the target genes taught by Oh *et al.* from claim 1 and the cancellation of any dependent claim specifying oligonucleotides complementary to such target gene. Finally, the rejection over Zhenghong *et al.* in view of Ono *et al.* has been overcome by removal of the target region taught by Zhenghong *et al.* from claim 1 and the cancellation of any dependent claim specifying oligonucleotides complementary to such target region.

None of the cited references discloses or suggests targeting a region of secondary structure within the HBV genome. As the Examiner has noted in related case Serial No. 08/463,624 (see Office Action in that case mailed 29 November 1996 at page 12), the prior art actually teaches away from such targeting of the epsilon region. Applicants thus respectfully submit that the claimed oligonucleotides complementary to to a region of secondary structure in the epsilon region of the HBV genome are thus nonobvious and patentable over the prior art references of record. Accordingly, Applicants respectfully request that all of the prior art rejections of record be withdrawn.

CONCLUSION

For the reasons set forth above, claims 1, 8-20, 36, 40-51 and 207-225 are now believed to be allowable. If the Examiner believes that any discussion of this communication would be helpful, she is invited to contact the undersigned attorney by telephone at (617) 526-6250.

Respectfully submitted,
HALE AND DORR LLP

By: 
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